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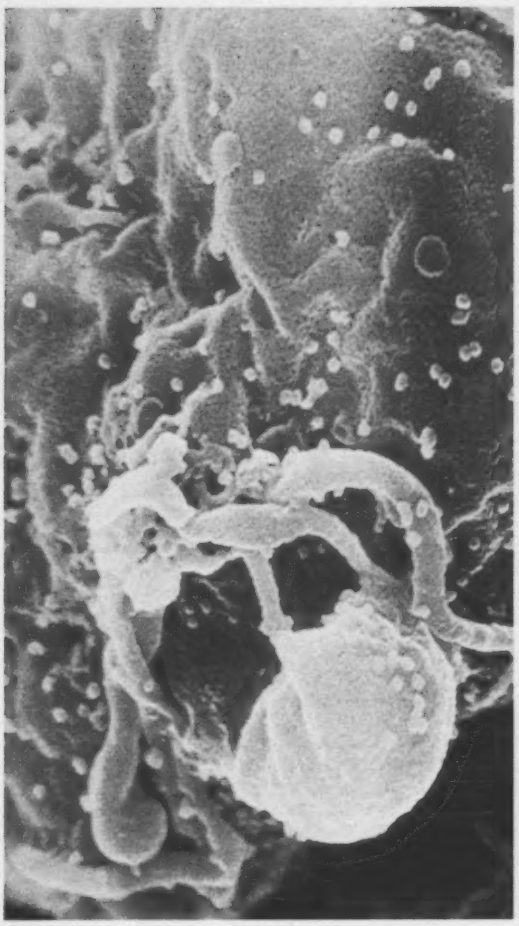
CANADA COMMUNICABLE DISEASE REPORT

UPDATE ON STIs



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CANADA COMMUNICABLE DISEASE REPORT

The Canada Communicable Disease Report (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public-health professionals, and policy-makers to inform policy, program development and practice.

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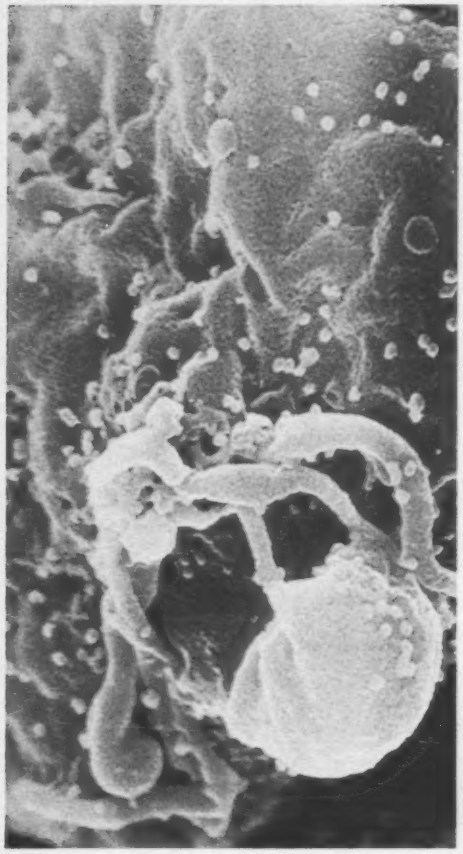

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Are enteric infections sexually transmitted in British Columbia?

Swastika N[1]*, Galanis E[2], BC STEI Group[3]

Abstract

Background: Enteric infections may on occasion be sexually transmitted, particularly among people who engage in oral-anal sexual contact. Although outbreaks of enteric infections have been reported among men who have sex with men (MSM) in British Columbia (BC), the epidemiology of sexually transmitted enteric infections has never been assessed.

Objective: To describe the epidemiology of enteric infections in BC to determine if sexual transmission may be occurring.

Methods: A descriptive analysis was conducted of all reported cases of shigellosis, amebiasis and giardiasis in BC for the period 2003–2012.

Results: For shigellosis and amebiasis, there was a high male-to-female ratio and a higher rate of infection in males aged 20-59 years as compared to all other age-sex groups. Additionally, for shigellosis, adult males were significantly more likely than females to acquire disease locally (RR 1.9; CI 1.7—.4).

Conclusion: Analysis suggests that sexual transmission of enteric infections, particularly shigellosis and amebiasis, may be occurring in MSM in BC. Further studies are indicated.

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Introduction

Enteric pathogens are most commonly transmitted through consumption of contaminated food or water (1-3). However, some enteric pathogens can also be transmitted through sexual practices involving fecal-oral contact, such as oral-anal, oral-genital and anal-genital intercourse (4-6). Although these sexually-transmitted enteric infections (STEIs) can occur in heterosexual individuals who engage in unprotected anal sexual contact, they are more common in men who have sex with men (MSM) than any other adult populations (4,5,7-9).

Pathogens transmitted sexually include *Entamoeba histolytica, Giardia lamblia, Shigella* (3,5,7,10-12), *Salmonella* (13) and Campylobacter (14). However, *Entamoeba histolytica, Giardia lamblia* and *Shigella* are most commonly STEIs (8,15,16). Inadvertent ingestion of minute amounts of feces containing as few as 10–100 organisms of *Shigella bacteria, Entamoeba histolytica* or *Giardia lamblia* cysts, during oral-anal sexual contacts could deliver a sufficient dose to cause infection. This low infectious dose also explains the tendency of these three pathogens to easily spread from person-to-person (7,17,18).

The incubation period for shigellosis is short; one to two days. It is characterized by diarrhea (which may be bloody and contain pus), fever and tenesmus, and is usually a self-limiting infection (12). Although 90% of *Entamoeba histolytica* infections are asymptomatic, fever, diarrhea and abdominal cramps can occur two to four weeks after exposure to the parasites. The infection resolves with treatment in two weeks (12). Giardiasis is usually asymptomatic in humans but may produce low-grade fever, foul-smelling diarrhea and abdominal cramps and bloating, one to two weeks after exposure. Symptoms usually last one to three weeks and people with healthy immune systems normally clear the infection on their own. Treatment may be required for immunocompromised patients (12,19).

Shigellosis, amebiasis and giardiasis are reportable communicable disease in British Columbia (BC). While past reports have highlighted outbreaks of shigellosis among the MSM population in BC (20,21,22), the epidemiology of STEIs, including shigellosis, has never been assessed in BC and is therefore not well understood. The objective of this study was to describe the epidemiology of these three infections in BC to determine if sexual transmission may be occurring and to identify the population and regions at risk of STEI.

Methods

A retrospective descriptive analysis was conducted of shigellosis, amebiasis and giardiasis cases reported in BC for the period 2003-2012. All cases were laboratory-confirmed and identified from the Integrated Public Health Information System (iPHIS). Exposure information including sexual activity and travel history was reviewed for all cases. Travel information was obtained from the Primary Access Regional Information Systems (PARIS) for Vancouver Coastal Health Authority cases and from iPHIS for the remaining health authorities. Travel information was classified as either "international travel" (if travel outside of Canada was reported within four days of symptom onset) or "local" (if the case reported no travel, or travel within Canada, within BC, or within the health authority of residence) (23). Exposure information was available only for shigellosis and amebiasis as giardiasis cases are not routinely followed-up by public health authorities in BC. Information on outbreaks was obtained from the Canadian Network for Public Health Intelligence outbreak summary module, BC Centre for Disease Control outbreak investigation reports and discussion with experts.

Statistical analyses included case counts and incidence rates (IR) by year, geography, sex and age groups. Population estimates for IR calculation were obtained from BC Stats (available at: http://www.bcstats.gov.bc.ca). Cases were grouped into one of four age groups. The 20-59 year age group represented the sexually active population because it was appeared to have an excess number of adult male cases in the preliminary analysis.

Data were analyzed using Microsoft Excel® 2007 and OpenEpi software (version 2.3.1). Chi square tests were used to compare proportions of shigellosis cases associated with international travel to that of local cases. A p - value of <0.05 was considered to be significant. Relative risk with 95% confidence intervals was calculated to compare the risk of shigellosis in these two groups.

Table 1: Characteristics and incidence rates (IR) per 100,000 population for reported cases of giardiasis, amebiasis and shigellosis in British Columbia, 2003–2012

Characteristics	Giardiasis (IR[number])	Amebiasis (IR[number])	Shigellosis (IR[number])
Provincial average annual IR	15.2 (6,593)	7.7 (3,359)	4.6 (1,986)
Sex[1]			
Female	12.1 (2,648)	4.2 (928)	3.7 (806)
Male	18.3 (3,933)	11.2 (2,422)	5.5 (1,176)
Male : female	1.5:1	2.6:1	1.5:1
Age group (males + females)			
0 to 9 years	26.9 (1,184)	4.1 (159)	4.8 (200)
10 to 19 years	10.0 (534)	3.9 (189)	2.5 (131)
20 to 59 years	16.6 (4,177)	11.2 (2,542)	5.9 (1,393)
60+ years	7.9 (698)	6.1 (469)	3.2 (262)
Health authority			
Fraser Health Authority	16.4 (2,496)	7.8 (1,199)	4.6 (705)
Interior Health Authority	10.7 (757)	1.2 (89)	1.8 (127)
Northern Health Authority	9.8 (279)	0.2 (5)	1.2 (34)
Vancouver Coastal Health Authority	20.4 (2,225)	16.2 (1,768)	8.2 (894)
Island Health Authority	11.4 (836)	4.0 (298)	3.1 (226)
Age group 20-59 years[1]			
Female	12.6 (1,592)	5.6 (630)	4.6 (541)
Male	20.6 (2,578)	16.7 (1,905)	7.3 (848)
Male-to-female ratio	1.6:1	3.0:1	1.6:1

[1] Two transgendered cases not included

Figure 1: Distribution of shigellosis cases by age category and sex for British Columiba, 2003–2012

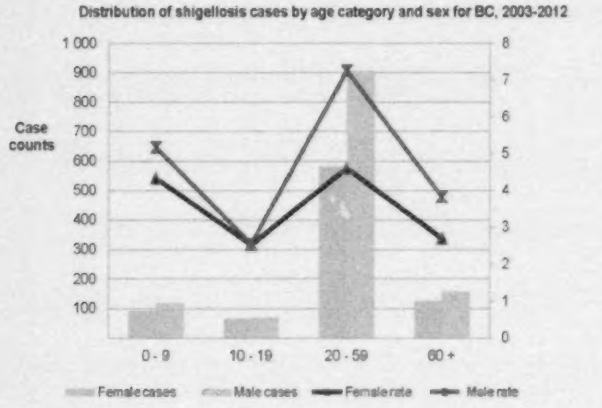
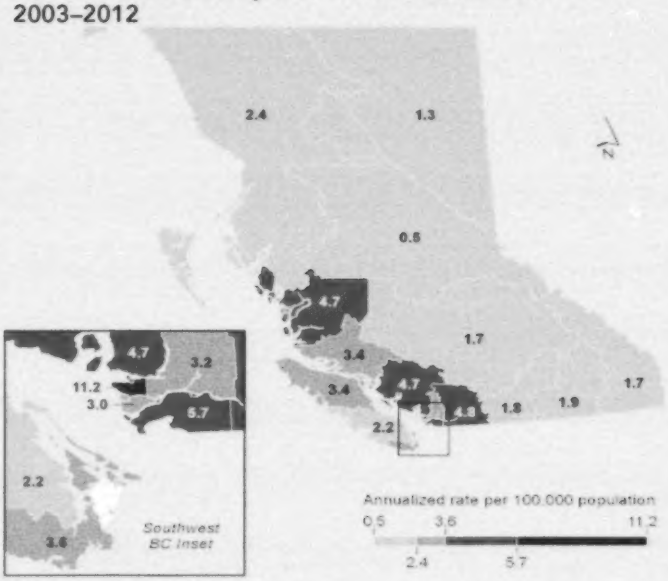


Figure 2: Shigellosis average annual incidence rate by health service delivery area in British Columbia, 2003–2012



Results

Overall, Vancouver Coastal Health Authority reported the highest average annual IR for all three infections, followed by Fraser Health Authority, Island Health Authority, Interior Health Authority and Northern Health Authority (**Table 1**). A higher male-to-female ratio was observed for all three infections in all health authorities; however, the majority of shigellosis and amebiasis was reported in those 20-59 years of age (5.9 and 11.2 per 100,000 population) and for giardiasis in children aged 0-9 years (26.9 per 100,000 population).

The average annual IR for shigellosis was 4.6 per 100,000 population (**Table 1**). The annual IR fluctuated with peak rates seen in 2003, 2005 and 2007. A declining rate was observed, from 6.3 in 2007 to 3.8 per 100,000 population in 2012 (data not shown). Overall, rates were higher in males than females (male-to-female ratio of 1.5:1), with highest IR among males aged 20-59 years (7.3 per 100,000 population) (**Figure 1**). Vancouver health services delivery area reported the highest average annual rate at 11.2 per 100,000 population (**Figure 2**).

Four shigellosis outbreaks were reported during 2003–2012. The first two outbreaks were caused by *Shigella sonnei* in 2007 and occurred in the Vancouver health services delivery area and Fraser Health Regions. The first outbreak occurred in the early part of 2007 and affected the MSM population and the second outbreak due to a different *Shigella sonnei* strain occurred in the latter part of 2007 and affected the homeless population (22). A third outbreak of *Shigella sonnei* linked to a local restaurant occurred in 2010 in the Okanagan health service delivery area (20). The final outbreak, due to *Shigella flexneri*, occurred during 2008-2012 and affected the MSM population in Vancouver health service delivery area (20).

Shigella sonnei (56.4%) was the most common strain reported in BC during 2003-2012, followed by *Shigella flexneri* (35.7%), *Shigella boydii* (5.1%) and *Shigella dysenteriae* (2.8%). Analysis demonstrated a shift in the dominating *Shigella* strain: during 2003-2008, *Shigella sonnei* was the prevalent infecting species (65.0%) in BC and during 2009–2012, *Shigella flexneri* was the prevalent infecting species (52.1%).

Limited exposure information was documented. In total, 58.0% of shigellosis cases, 15.1% of giardiasis cases and 8.3% of amebiasis cases had exposure information entered in iPHIS. Of these, less than 1% mentioned sexual activity as an exposure. During 2008–2012, 928 shigellosis cases were reported to PARIS and iPHIS, 654 cases (70.5%) of these had travel information documented, and 461 cases (70.4%) reported international travel. Overall, males were at a greater risk of acquiring shigellosis locally compared to females (RR 1.6; CI 1.4-1.8). Among the 20-59 year age group, males were at greater risk of acquiring shigellosis locally compared to females (RR 1.9; CI 1.7-2.4).

The average annual IR of amebiasis in BC was 7.7 per 100,000 populations (**Table 1**). Rates were higher in males than females across all age groups (male-to-female ratio of 2.6:1); with highest IR among males aged 20-59 years (16.7 per 100,000 population). Vancouver Coastal Health Authority reported the highest rate (16.2 per 100,000 population). No outbreaks were reported during the study period.

The average annual IR of giardiasis in BC was 15.2 per 100,000 population (**Table 1**). Vancouver Coastal Health Authority reported the highest average annual IR (20.4 per 100,000 population). The IR was higher in males than females across all age groups (male:female ratio of 1.5:1), with the highest IR observed in males aged 0-9 years (28.9 per 100,000 population)

(data not shown). No outbreaks were reported for the study period.

Discussion

The results of this study demonstrate higher rates of all three infections in Vancouver Coastal Health Authority region, with a higher male-to-female ratio. However IR was the highest in adult males for shigellosis and amebiasis and in children (0-9 years) for giardiasis. The higher rates in adults (for shigellosis and amebiasis) may be due in part to sexual transmission.

For shigellosis and amebiasis, a high male-to-female ratio was noted, with a higher rate of infection in males aged 20–59 years as compared to all other age-sex groups. Additionally, for shigellosis, adult males were significantly more likely than females to acquire shigellosis locally and an excess of shigellosis cases in adult males was observed in Vancouver health services delivery area (data not shown). Furthermore, two of the four shigellosis outbreaks reported in BC affected the MSM population. In both outbreaks, no other common risk factors such as food, restaurants or travel were noted and sexual practices (oral-anal sex) were thought to be the mode of transmission. This is in contrast to giardiasis which affected males more than females across all age groups with the highest rate reported in males aged 0-9 years which is less indicative of sexual transmission.

In Canada, other outbreaks of shigellosis where sexual transmission was implicated have been reported. In 1999-2001 an outbreak of *S. sonnei* and *S. flexneri* affected the MSM population in Quebec (24,25) and in July 2014, a cluster of shigellosis cases was reported among MSM in Toronto. Outbreaks of shigellosis affecting MSM populations are reported by many developed countries (26-33). In MSM populations, shigellosis is predominantly a sexually-transmitted infection (15), with the greatest risk of transmission associated with sexual practices involving direct oral-anal contact (7,8,15,25,27,31). Additionally, having multiple sexual partners could be responsible for widespread dissemination of *Shigella* in MSM (34). Human immunodeficiency virus infection has also been identified as an important risk factor for shigellosis in MSM (7,15,27).

Analysis demonstrated a shift in the dominant infecting *Shigella* species (*Shigella sonnei* to *Shigella flexneri*) around 2009. Wilmer et al. (20) reported similar findings in a study where *Shigella flexneri* became the dominant circulating strain in the MSM population within Vancouver City Centre after 2008. Others have also reported a change in the dominant *Shigella* species in the same MSM population (27,35,36). These shifts may reflect some degree of herd immunity towards a given *Shigella* species (7).

This study also found that adult males were more likely than adult females to acquire shigellosis locally (RR = 1.9). A similar finding was reported in a shigellosis outbreak in Wales, where locally acquired shigellosis occurred predominantly in males who had reported MSM activity in the week before illness (33).

A higher risk of travel in female cases is indicative of acquiring shigellosis via risk factors considered to be more common during travel including contaminated food and water.

The highest annual average incidence for amebiasis was reported in adult males (16.7 per 100,000 population). The reasons for this are unclear. There was very little sexual exposure information on amebiasis. *Entamoeba histolytica* is usually transmitted from person-to-person (10) or via contaminated water (12). Since most British Columbians have access to safe drinking water (37), apart from travel to endemic countries, sexual transmission seems likely for this age-sex group. Sexual transmission of *E. histolytica* has been reported in the MSM population, with oral-anal sexual practices considered to be the mode of transmission (16,38,39).

The rate of giardiasis was higher for males in all age groups, with males aged 0-9 years having the highest rate. This finding is similar to observations reported by other developed countries (40-43), where *Giardia* most commonly infected small children in day-care centres and transmission was associated with poor hand hygiene. Given a similar pattern of giardiasis in BC, sexual transmission of *Giardia* seems less likely, or may be occurring at low rates, or is being overwhelmed by other transmission routes such as contact with contaminated water, travel to endemic countries and transmission in day-cares centres (40).

While this study has demonstrated a higher incidence of some enteric infections in males aged 20-59 years, not all adult male excess disease can be attributed to sexual transmission and not all sexual transmission will be observable by an excess in adult males. The combination of adult age and male sex used to identify an at-risk population is not a specific indicator of sexual transmission. Other factors (such as contaminated water, occupational and outdoor recreational exposure) may also account for the highest incidence observed in this group. Additionally, heterosexual adults are also at risk of STEI through oral-anal contact. Missing exposure information due to the lack of case interviews, incomplete assessment of sexual risk factors or incomplete data entry further hampered the ability to attribute cases to a specific transmission route.

Despite growing literature on the risk of STEIs, prevention guidelines and educational information for at-risk populations are not widely available. Public health guidelines on this topic do not appear to be available in Canada. Such guidelines could address the public health investigation required to better assess the risk of STEIs and modes of transmission, the need for contact tracing and educational messaging recommended for cases, at-risk populations and the general population. The findings of this study led to a review of the provincial enteric case follow-up forms to better capture information about sexual practices that increase the risk of STEIs.

A timely diagnosis and treatment of enteric infections will not only decrease the duration of illness but also interrupt its transmission (4,29). Currently, the *Canadian Guidelines on Sexually Transmitted Infections* recommend that health care providers test for enteric pathogens if clients report anorectal sexual activities and/or present with compatible symptoms (4). Additionally, health care providers should provide safe

sex counseling based on a personalized sexual health risk assessment (29). Currently, intense efforts to educate the at-risk population have been reported only during STEI outbreaks (27,44). However, to increase awareness about STEIs among at-risk populations, sexual health promotion messaging needs to occur on a more routine basis and should include information about STEIs, advice on avoiding unprotected oral-anal contact (especially if the partner is sick), hand hygiene following sexual contact and to seek medical advice for gastroenteritis (15,31).

Conclusion

This study suggests that sexual transmission of enteric infections, in particular shigellosis and amebiasis, may be occurring among MSM in Vancouver, BC. This conclusion is supported by outbreak data and limited case exposure (sexual activity, travel) history. To reduce the incidence of STEIs, public health interventions should expand beyond safe food and hand hygiene practices. Continued surveillance especially of case exposure history may also help to guide public health interventions to reduce STEI.

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Conflict of interest

None.

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SYSTEMATIC REVIEW

Benzathine penicillin G for the management of early syphilis among HIV co-infected persons: A systematic review

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Abstract

Background: The optimal treatment for syphilis in people who are human immunodeficiency virus (HIV) positive is controversial.

Objective: To assess the efficacy of three doses versus a single dose of long acting Benzathine Penicillin G (BP-G) for the effective management of early syphilis among HIV co-infected populations.

Methods: A systematic search of the published literature was conducted using MEDLINE and EMBASE databases to identify clinical and observational studies published between January 2010 and May 2015. Inclusion criteria were: publication in English or French, populations co-infected with HIV and early syphilis, treatment with BP-G and outcomes related to syphilis treatment. All articles underwent a risk of bias assessment and data extraction was completed on all included studies.

Results: Seven studies were eligible for final inclusion, data extraction and analysis. The evidence from the final included studies were from non-randomized controlled trials. In general, no significant differences were found between groups treated with one versus two or more doses of BP-G; but there was a trend toward longer time to treatment failure with three doses. Differences in methodology limit the ability to draw any firm conclusions on the relative efficacy between these two treatment regimens.

Conclusion: Insufficient data exist to ascertain whether or not there is an added benefit from additional doses of BP-G for the treatment of early syphilis with HIV co-infection. A high-quality, randomized controlled trial is needed to definitively nswer this question.

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Introduction

The effective management of early syphilis (primary, secondary and early latent stages) among human immunodeficiency virus (HIV) co-infected persons is an important public health issue due to the resurgence of syphilis in Canada and globally (1-5). Between 2000 and 2012, the rate of infectious syphilis in Canada increased from 1.84 to 8.85 cases per 100,000 persons (4). Similar increases were also noted in Europe and the United States (1,5).

The prevalence of early syphilis is higher among HIV co-infected persons than in the general population (6-8). In addition, case reports and case series suggest that co-infection with HIV can result in atypical or more severe manifestations of syphilis. HIV-positive persons are more likely to present with multiple, larger ulcers, primary and secondary infections can overlap and cerebrospinal fluid (CSF) abnormalities, ocular and ophthalmologic manifestations are more common (9-13). Intercurrent syphilis may also temporarily increase HIV viral load and reduce CD4 lymphocyte count (14,15).

Furthermore, the optimal treatment for HIV-positive individuals co-infected with early syphilis has been controversial since early reports of treatment failures in the late 1980s which followed standard recommended treatment regimens (16). Since that time, a number of studies have been completed, but their small sample sizes, largely observational nature and methodological heterogeneity, has prevented the development of strong evidenced-based recommendations about optimal treatment in this situation. Current guidelines have been criticized for not guiding physicians (17) and ambiguity in recommendations has

resulted in varied clinical practice (18). As a result, the optimal antibiotic regimen among individuals with early syphilis remains controversial and, at times, the guidance is unclear (19,20).

Findings from a systematic review published in 2011 suggest that inadequate high-quality evidence exists to fully understand the efficacy of additional doses of BP-G for the management of early syphilis in individuals with HIV as measured by serologic response to treatment (19,20). Further, it is unclear whether improved outcomes would be achieved from additional doses of BP-G and whether this would outweigh the requirement of individuals to adhere to additional painful injections scheduled over multiple clinical visits (19).

In order to address these issues, a systematic review of recent evidence was carried out to compare the efficacy of one versus three doses of BP-G in the treatment of adults with HIV and early syphilis infection.

Methods

Search strategy

A search of the published literature was conducted using the following electronic databases: MEDLINE, EMBASE, Cochrane Library, Clinical trials.gov, Canadian Agency for Drugs Technologies in Health and Scopus. Hand searches were also completed to identify any relevant studies that may have been missed in the initial search. Key words used for the search were: "syphilis" or "*Treponema pallidum*", "human immunodeficiency virus" or "HIV" and "follow-up" or "treatment".

Eligibility criteria

Eligibility criteria were designed to update a previous systematic review published in 2011 (19). Studies were eligible for inclusion if they were published between January 2010 and May 2015 in English or French. Studies were required to report upon early syphilis in adult populations who are HIV-positive and interventions comparing doses of BP-G. All eligible articles were required to report outcomes related to the biologic cure of early syphilis.

Study selection

A two-step process was used to exclude l ess relevant publications. Two authors (ON, SH) independently screened titles followed by abstracts. Any discrepancies were resolved in discussion with a third author (LP). Publications were excluded if they did not have the following key words: "HIV" or "human immunodeficiency virus" and "early syphilis" and "treatment" or "antibiotic" or "management" or "follow-up" or "therapy".

An a priori decision was made to use the ACROBAT-NRSI to assess risk of bias in included observational studies (21), the Cochrane risk of bias assessment tool for randomized controlled studies (RCT) (22) and for the accessing methodological quality of systematic reviews (AMSTAR) (23). Overall quality appraisal of each study was performed by two reviewers (ON, SH) and a third author (LP) was consulted to resolve any disagreement.

Data extraction

Two authors (ON, SH) extracted information on the study design, target population, sample size and intervention. The lack of consistency of reported data did not allow for meta-analysis. Therefore, results were summarized in a narrative format.

Results

A total number of 328 citations were identified through different databases and hand searches (**Appendix 1**). After the title screening, 21 citations were retained for abstracts screening. Finally, seven publications were excluded based on language (24), study design (25,26) or absence of treatment data (27-30). The remaining 14 studies were eligible for full text retrieval. Seven studies were excluded for the following reasons: not early syphilis (31-33) or unspecified treatment information (34-36). Seven final publications were included for data extraction and synthesis. Key characteristics of the included studies are reported in **Table 1** (excludes two systematic reviews).

Study Characteristics

Among the included publications, there were two systematic reviews and five studies of observational design (two prospective cohort studies and three retrospective studies). The systematic review by Blank et al. was focused on HIV co-infected population (19); however, the review by Clement et al., focused more broadly on syphilis with some discussion of HIV co-infection (20). Studies were conducted in Taiwan (37), the United States (38) and Europe (39-41). The participants in the studies were predominantly male. In four studies, the intervention was one or three doses of BP-G (37,39-41). A single study compared one dose of BP-G with two or more doses of BP-G (38) (**Table 1**).

Risk of bias of included studies

There were no high-quality intervention studies available to include in the update and therefore the overall body of evidence includes important biases (**Table 1**). The possibility of the introduction of selection biases through lack of randomization is important. Of additional concern, the publications generally did not adjust for the known confounder of HIV treatment status or other comparable measures (e.g., CD4 count). In addition, the publications often did not stratify participants by stage of syphilis and HIV status (including treatment) and there were often considerable missing data (**Table 2**).

Table 1. Characteristics of included studies

Author	Number[1]	Country of study	HIV treatment	Pharmacological regimen	Follow-up period	Outcome measure
Cousins (39) 2012	62 (3 dose) Unclear (1 dose)	United Kingdom	Unspecified: Some patients receiving antiretroviral therapy (ART)	1 dose: BP-G 2.54 MU versus 3 doses: BP-G 2.4 MU	12 months	Serological cure (4-fold decrease in serum RPR or serofast for 12 months)
Knaute (40) 2012	88	Switzerland	Not specified	1 dose: BP-G 2.4 MU versus 3 doses: BP-G 2.4 MU	3, 6, 8, 9, 12, 18, 24 months	Serological Response (VDRL, TPPA, Pathozyme IgM)
Tittes (41) 2013	84	Austria	44% (35/80) were on ART	1 dose: BP-G 2.4 MU versus 3 doses: BP-G 2.4 MU	3, 6 and 12 months	Serological cure (4-fold decrease in VDRL within 6 months) Time to cure (days)
Yang (45) 2014	420	Taiwan	63.2% (362) on combination ART	1 dose: BP-G 2.4 MU versus 3 doses: BP-G 2.4 MU	6 and 12 months	Serological response (4-fold decrease or greater in RPR titres at 12 month follow-up)
Ganesan (38) 2015	286 (393 infections[2])	United States	59% used Highly active retroviral therapy (H) at first syphilis case	1 dose: BP-G2.4 MU versus ≥2 doses: BP-G 2.4 MU	3, 6, 9, 12, 18, 24 months	Serologic response Seroconversion

Abbreviations: BP-G, benzathine penicillin G; HIV, human immunodeficiency virus; IgM, immunoglobulin M; MU, million units; RPR, rapid plasma regain test; VDRL, Venereal Disease Research Laboratory test; TPPA, *Treponema pallidum* particle agglutination assay.

1 Number of study participants analyzed and not necessarily the total number of infections

2 Reflects the number of cases as some study subjects contributed more than one infection

Outcomes

Overall, four observational studies not included in the 2011 and 2014 systematic reviews included sample sizes of 62 to 350 subjects and concluded that there were no differences in serologic response at 12 (n=2 or 3 studies) or 24 months (n=1 study) if one or three doses BP-G were given (38-41). The fifth and largest, observational study conducted to date (n=573) in Taiwan hypothesized that one dose was not inferior to three weekly doses of BP-G and set the significant difference between regimens as 10% of participants with a serologic response at 12 months. Yang et al. were unable to demonstrate that one dose was not inferior to three doses of BP-G (37).

Serologic response

Serologic response to syphilis treatment is monitored by serial testing using the rapid plasma reagin (RPR). The RPR is a non-specific test that detects both IgM and IgG antibodies and is a measure of response to treatment (42). In the included studies, serologic response was commonly defined as ≥4 fold reduction in RPR titres at 12 months.

Among the included publications, four did not show a benefit from additional doses beyond the standard therapy of 2.4 million units in a single dose of BP-G (37,39-41,43). Yang et al.'s study was suggestive of a positive effect from additional doses: The effect was statistically significant when analyzed by last known results ($p = 0.04$) but not when analyzed per protocol ($p = 0.24$) (37).

The time to the first episode of serological failure appeared shorter in the group that received one dose: 1,184 (40 months) days for one-dose group and 1,436 days (almost 48 months) in the three-dose group, suggesting benefit from a three-dose regimen (37). In the same study, a Kaplan-Meier survival plot model showed a statistically significant longer mean time to failure in the group that received three-dose regimen ($p=0.03$) (37).

HIV status

Co-infection with HIV impacts the manifestations and potential response to treatment of early syphilis. Therefore, the use of anti-retroviral therapy is an important characteristic to include when assessing the efficacy of syphilis therapy. Tittes et al. found a slower response to one-dose therapy within an HIV-positive group compared to an HIV-negative group, but there was no significant benefit when the two groups were treated with the three-dose regimen (41). Ganesan et al. found similar findings when comparing populations with CD4 <500 cells/μL compared to CD4 ≥ 500 cells/μL ($p=0.012$) and the Knaute et al. publication reported a statistically

Table 2: Summarized results for single and multiple doses of benzathine penicillin G for early syphilis in HIV co-infected persons from observational studies.

Author	BP-G doses[1]	Serological response[2] at 12 months		HIV association with serological response	
		Response	*p* value	Response	*p* value
Cousins (39) 2012	1 dose	78.9% (95% CI 68.0-89.8)	$p > 0.05$	N/A	
	3 doses	64.1% (95% CI 45.0-73.2)		N/A	
Knaute (40) 2012	1 dose	100%		HIV-negative (reference)	
	3 doses	100%		CD4 ≥500 HR 1.27 (95% CI 0.79-2.04) CD4 < 500 HR 0.83 (95% CI 0.60-1.14)	$p = 0.332$ $p = 0.241$
Tittes (41) 2013	1 dose	88%		No correlation between viral suppression and outcome – data not shown	$p = 0.18$
	3 doses	97%			
Yang (45) 2014	1 dose	66.2% (95% CI 59.6–72.4)	$p = 0.24$	CD4 ≤ 200 (reference)	
	3 doses	71.8% (95% CI 64.7–78.2)		200 < CD4 ≤ 350 OR_{ADJ} 1.05 (95% CI 0.54-2.07) CD4 > 350 OR_{ADJ} 1.51 (95% CI 0.69-3.51)	$p = 0.88$ $p = 0.30$
Ganesan (38) 2015	1 dose	92%		CD4 (per 100-cell increase) HR 1.07 (95% CI 1.01-1.12)	$p = 0.02$
	≥2 doses	92%			

Abbreviations: BP-G, benzathine penicillin G; CD4, cluster of differentiation; CI, confidence interval; HIV, human immunodeficiency virus; HR; higher rate; OR_{ADJ}, odds ration adjusted.

[1] Dose = 2.4 million units BP-G IM in a single dose

[2] Proportion of subjects who exhibited response to therapy defined as a ≥4-fold decline in nontreponemal titre

significant association between higher CD4 count and time to response to therapy (38,40).

Harms

The included publications did not document harms of therapy. Up to 10% of the population will report allergies to penicillin (44), potentially posing challenges to the use of BP-G. In addition, the intramuscular route of administration is painful and the additional health care visits are a potential burden to both the health care system as well as the patient.

Discussion

This review confirms that there is limited evidence to definitively guide management decisions in HIV-infected persons with early syphilis infection. The foundational 2011 systematic review concluded that the optimal treatment regimens remain unknown (19) and, although limited in its focus on HIV-positive individuals, the 2014 systematic review (20) concluded that in the absence of compelling data, individuals with HIV infections should be treated similarly to uninfected patients. This review of additional studies not included in these systematic reviews is consistent with the recommendation to use single-dose BP-G for HIV co-infected patients based on serologic response as the treatment outcome.

Of note, however, was the finding by Yang et al., which suggested a possible benefit of three doses of BP-G by reporting a longer time to serologic treatment failure in this group (37). However, the authors described a number of limitations to the study that could potentially explain the difference in their findings relative to other studies: 1) the study was not a RCT; 2) the decision to use one vs three doses was made by physicians assessing the patients; 3) 25% had missing RPR titres on follow-up testing; 4) the researchers could not definitely differentiate between re-infection and treatment failure; and, 5) the majority of patients were men who have sex with men (MSM) which limited the generalizability of their findings to other populations. In later correspondence, the same authors reported that the proportion of HIV co-infected patients with early syphilis treated with three doses at the eight centres in Taiwan declined from 60.2% in 2007-2009 to 25% in 2012 after a change in the Centre for Disease Control and Prevention (CDC) guidelines recommending single-dose BP-G (45).

Finally, results suggested that individuals with the highest CD4 counts had lower risk of poor serologic response to treatment (40,45).

Strengths and limitations

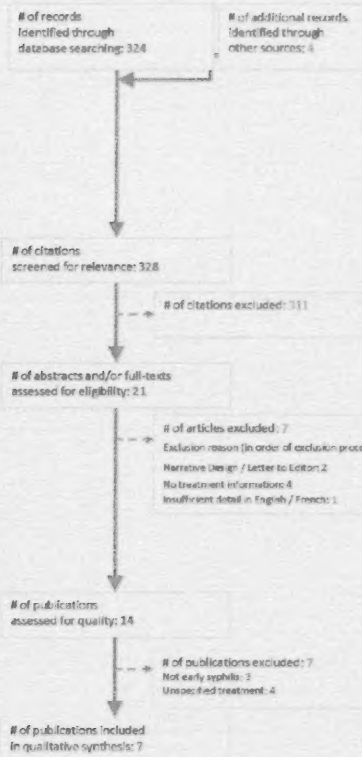
Strength of this review is that it is built on a previous systematic review and that it took all precautions to minimize bias. However, a number of limitations need to be considered when interpreting the results. Included studies were limited by their design and the potential impact of selection bias through the lack of randomization to dosing schedules contributes important potential biases to the results. The lack of adjustment for HIV treatment /status (anti-retroviral therapy and CD4 count) further limits the ability to extrapolate results to the

clinical setting. These are known and significant associations (37) but the included publications were not analyzed with a stratified or multivariate approach (37,39-41). Studies were not representative of the entire population at risk for syphilis and HIV co-infection. More than 80% (and as high as 99%) of included study participants were male, of which the majority appeared to be MSM. Ideally, an adequately-powered RCT with clearly stratified HIV populations including women and with sufficiently long follow-up periods should be conducted to more definitely answer this question.

Conclusion

Our review found that the recent publications do not demonstrate a clear benefit to additional doses of BP-G for the treatment of individuals with early syphilis and HIV co-infection; more definitive trails are needed.

Appendix 1: Inclusion and exclusion of publications


# of records identified through database searching: 324
# of additional records identified through other sources: 4
# of citations screened for relevance: 328
# of citations excluded: 311
# of abstracts and/or full-texts assessed for eligibility: 21
# of articles excluded: 7
Exclusion reason (in order of exclusion process):
Narrative Design / Letter to Editor: 2
No treatment information: 4
Insufficient detail in English / French: 1
# of publications assessed for quality: 14
# of publications excluded: 7
Not early syphilis: 3
Unspecified treatment: 4
# of publications included in qualitative synthesis: 7

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Conflict of interest

None to declare.

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Does suppressive antiviral therapy for herpes simplex virus prevent transmission in an HIV-positive population? A systematic review

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Abstract

Background: Among individuals with genital herpes simplex virus (HSV), co-infection with human immunodeficiency virus (HIV) hs been shown to increase the frequency and severity of HSV symptoms, HSV shedding, and risk of HSV transmission.

Objective: To assess whether suppressive antivirual therapy for genital HSV in an HIV-positive populatation prevents HSV transmission to a susceptible partner.

Methods: A systematic search of the literature was conducted using MEDLINE and EMBASE databases to identify randomized controlled trials published between January 2005 and June 2015. Inclusion criteria were trials written in English or French utilizing suppressive antiviral therapies for HSV. Studies had to report on outcomes related to HSV transmission from HIV-positive populations. Surrogate markers of HSV transmission risk, such as HSV detection and viral load, were also included. Articles underwent a risk of bias assessment, and those with low risk of bias underwent data extraction to complete a narrative synthesis.

Results: This review identified thirteen papers. Only one study directly measured transmission of HSV. The overall transmission rate was <10%, and suppressive antiviral therapy had no significant protective effect (9% transmission rate in the acyclovir group vs. 6% in the placebo group; hazard ratio [HR]: 1.35, 95% CI: 0.83–2.20). The remaining 12 papers addressed surrogate markers of transmission risk: HSV detection and viral load. Suppressive acyclovir appears to be effective in reducing HSV detection among HIV-positive populations, but it does not appear to reduce viral load. Suppressive valacyclovir may be effective in reducing HSV detection and viral load among HIV-positive patients who are antiretroviral therapy (ART)-naïve, but its effect appears to be nullified among those concurrently on ART.

Conclusion: Based on current evidence, suppressive antiviral therapy may reduce HSV detection and viral load, but its impact on HSV transmission is unclear. Clinicians should caution HIV-positive patients with HSV that suppressive therapy may not reduce risk of HSV transmission to susceptible partners.

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Introduction

Approximately 14% of Canadian adults tested positive for genital herpes simplex virus (HSV) type 2 in 2009 (1). HSV is particularly widespread among people with human immunodeficiency virus type 1 (HIV), affecting 50% to 90% of the HIV-positive population (2).

Genital HSV reactivation has been shown to increase HIV viral load, enhancing risk of HIV transmission and HIV disease progression (3,4). In turn, HIV has been shown to increase the frequency and severity of HSV symptoms, HSV shedding, and risk of HSV transmission (5,6). Given this interaction between HSV and HIV, prevention of HSV transmission among HIV-positive populations is a significant public health concern. Minimizing rates of HSV co-infection among HIV-positive individuals could prevent increases in HIV viral load, HIV transmission, and HIV progression that characterize HSV and HIV co-infection. Preventing HSV transmission from HIV-positive partners to HIV-negative partners is also important to public health as HSV infection has been estimated to increase the risk of HIV acquisition three-fold (7).

Suppressive therapy with acyclovir, famciclovir, or valacyclovir is routinely used in populations co-infected with HSV and HIV. These agents have been shown to reduce HSV detection and viral load, which have been linked to a reduced risk of HSV transmission in immunocompetent populations (8,9). Of interest is whether these agents also reduce risk of HSV transmission in HIV-positive populations. The most recent reviews, published in 2007 (10,11) but neither were able to find sufficient literature to evaluate HSV transmission in HIVpositive populations.

The objective of this systematic review was to assess randomized controlled trials in the HSV and HIV co-infected population, focusing on the impact of suppressive HSV antiviral therapies on HSV transmission, HSV detection, and HSV viral load.

Methods

Search strategy

A systematic search of MEDLINE and EMBASE databases was conducted to find articles on randomized controlled trials published within the last 10 years; previous reviews included searches for literature published prior to this. The search strategy used MeSH terms for "treatment outcome" and "herpes simplex virus," along with relevant keywords (see text box).

#	Search strategy
1	exp treatment outcome/
2	drug efficacy/ or drug effect/
3	(effic* or outcome*).mp.
4	1 or 2 or 3
5	exp *herpes simplex/ or (herpes or HSV1 or HSV2 or HSV-1 or HSV-2 or HSV).tw.
6	4 and 5
7	limit 6 to (randomized controlled trial and last 10 years)

Eligibility criteria

Articles were eligible if they were written in English or French and had been published between January 2005 and June 2015 in peer-reviewed journals. Studies needed to report on genital HSV in HIV-positive adults (18 years or older) and describe a pharmacological intervention using a randomized controlled trial design. Articles were only included if the pharmacological comparison evaluated a suppressive treatment with at least one of the three most commonly used anti-HSV oral agents, acyclovir, famciclovir and/or valacyclovir. All eligible articles had to report on HSV transmission, detection, and/or viral load as outcomes. Studies that assessed topical treatments (e.g. gels or creams) were excluded due to their lack of availability outside the scope of clinical trials and the limited efficacy of the treatment. Studies in pregnancy and those that examined episodic treatments were outside the scope of the research question.

Study selection

Titles were screened and excluded if they were not related to HSV or HIV. Articles meeting this basic screening criterion were obtained for full-text review and assessed independently by two authors (CRS, UA) based on the eligibility criteria described above; a review resolved any discrepancies. References from relevant articles were screened and retrieved where appropriate. A formal quality assessment of each article meeting all the eligibility criteria was then performed independently by two authors (CRS, UA), using the Cochrane Collaboration's tool for assessing risk of bias (12). Studies with a high risk of bias were excluded.

Data extraction

Data were summarized by one author (CRS) in Microsoft Excel and then reviewed for accuracy and completeness by another (UA). Relevant data for each article included the patient population, country of study, pharmacological regimens, follow-up period, antiretroviral therapy (ART) status, CD4 cell count, number of transmissions of HSV (primary outcome), HSV detection and viral load (surrogate markers of transmission risk), effect measures, and adverse events.

The purpose of this review was to provide a narrative synthesis of the literature, so funnel plots and assessment of heterogeneity were not completed. A review protocol was not published for this review.

Results

A total of 492 papers were identified, 485 from databases and 7 through reference searches of relevant articles. Of these, 315 were unique. After screening and eligibility assessment, 14 studies remained to be assessed for risk of bias. One paper was excluded due to a high risk of bias (13) resulting in 13 papers being included in the systematic review (**Appendix 1**).

Study characteristics

The characteristics of the 13 studies are summarized in **Table 1**. Only one of the 13 studies directly measured HSV transmission (14). The remaining 12 papers focused on surrogate markers of transmission risk, that is, HSV viral detection and/or viral load. Of these, 7 studies addressed both HSV detection and genital HSV viral load (15,17,19,21-24), whereas 5 reported on HSV detection alone (16,17,19,23,24). All the studies utilized polymerase chain reaction (PCR) assays for both HSV detection and viral load.

The 13 clinical trials included 2,367 HSV and HIV co-infected participants. The majority of trials were conducted on populations in African countries (n = 7), and two were in Peru, two in the United States, and one in Thailand. One trial used a sample that spanned three continents. The majority of studies involved only female participants (n = 9), one used only males, and three included both sexes. Follow-up periods varied from 1 to 24 months. Eight studies included only participants who were

Table 1: Characteristics of suppressive antiviral therapy for herpes simplex virus in an HIV-positive population

Authors Year	Number[1]	Country of study	Pharmacological regimen	Follow-up months	HIV treatment	Outcome measure
Mujugira et al. (14) 2013	911 males and females	7 (eastern and southern African countries)	Acyclovir (400 mg bid) versus placebo	24	Not receiving Antiretroviral therapy (ART)	HSV-2 transmission
Baeten et al. (15) 2008	20 females	Peru	Valacyclovir (500 mg bid) versus placebo	2	Not receiving ART	Genital HSV-2 detection Genital HSV-2 viral load Adverse events
Cowan et al. (16) 2008	125 females	Zimbabwe	Acyclovir (400 mg bid) versus placebo	3	Not explicitly stated (however, ART was rarely available at the time of the study)	Genital HSV-2 detection
Delany et al. (17) 2009	300 females	South Africa	Acyclovir (400 mg bid) versus placebo	3	Not receiving ART	Genital HSV-2 detection Genital HSV-2 viral load Adverse events
Dunne et al. (18) 2008	67 females	Thailand	Acyclovir (800 mg bid) versus placebo	1	Not receiving ART	Genital HSV-2 detection
Kim at al. (19) 2010	76 males and females	South Africa, Zimbabwe, Zambia, Peru, United States	Acyclovir (400 mg bid) versus placebo	6	Not receiving ART	Genital HSV-2 detection Genital HSV-2 viral load
Nagot et al. (20) 2007	140 females	Burkina Faso	Valacyclovir (500 mg bid) versus placebo	3	Not receiving ART	Genital HSV-2 detection Adverse events
Ouedraogo et al. (21) 2006	60 females	Burkina Faso	Valacyclovir (500 mg bid) versus placebo	3	All patients receiving highly active antiretroviral therapy (HAART)	Genital HSV-2 detection Genital HSV-2 viral load
Perti et al. (22) 2013	34 males and females	United States	Acyclovir (400 mg bid) versus valacyclovir (1,000 mg bid)	3	Not receiving ART	Genital HSV-2 detection Genital HSV-2 viral load Adverse events
Tanton et al. (23) 2010	484 females	Tanzania	Acyclovir (400 mg bid) versus placebo	24	Not explicitly stated (Free ART became available in regional and district hospitals in the study area during the trial)	Genital HSV-2 detection Genital HSV-2 viral load Adverse events
Tobian et al. (24) 2013	96[1] females	Uganda	Acyclovir (400 mg bid) versus placebo	24	All patients receiving ART	Genital HSV-2 detection Genital HSV-2 viral load
Van Wagoner et al. (25) 2015	34[2] females	United States	Valacyclovir (1,000 mg qd) versus placebo	6	All patients receiving ART	Genital HSV-2 detection Adverse events
Zuckerman et al. (26) 2007	20 males	Peru	Valacyclovir (500 mg bid) versus placebo	2	Not receiving ART	Genital HSV-2 detection Adverse events

Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type-1; HSV-2, herpes simplex virus type-2

[1] 440 subjects were enrolled, but only 96 were assessed for genital HSV-2 detection/genital HSV-2 viral load
[2] 101 subjects were enrolled, but only 34 were assessed for genital HSV-2 detection

ART-naïve, three included only individuals receiving ART, and two did not explicitly state ART status. Most trials either compared suppressive acyclovir (400 mg bid or 800 mg bid) to placebo (n = 7) or suppressive valacyclovir (500 mg bid or 1,000 mg qd) to placebo (n = 5). One study compared suppressive acyclovir (400 mg bid) to high-dose suppressive valacyclovir (1,000 mg bid). None of the studies used famciclovir. All clinical trials were evaluated to be of low risk of bias.

HSV-2 transmission

HSV-2 transmission was only directly measured in one study, a well-designed trial where 911 sero-discordant heterosexual couples were followed for 24 months (14). Infected partners were HSV positive and HIV positive (not on ART) and were randomized to either suppressive treatment (acyclovir 400 mg bid) or placebo. Susceptible partners were HSV negative and HIV negative. In this study, suppressive acyclovir did not reduce transmission of HSV when compared with placebo. Transmission occurred in 9% (40/458) of the treatment group and in 6% (28/453) of the placebo group (hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 0.83–2.20). HSV transmission was two times higher from males to females than from females to males.

HSV-2 detection

Twelve studies reported on genital HSV detection. These studies utilized PCR and reported the percentage of participants, visits, or swabs/samples that were positive for HSV.

Acyclovir versus placebo

Six clinical trials that reported on HSV detection compared suppressive acyclovir to placebo (**Table 2**). Five of the six trials used a standard dose of acyclovir (400 mg bid) (16,17,19,23,24), whereas one had a higher dose of 800 mg bid (18). Overall, four of the six studies found a statistically significant effect of suppressive acyclovir treatment on HSV detection; two studies with ART-naïve patients (17,18) one with patients who initiated ART at study commencement (24), and one where ART status mg bid dose appeared to have greater efficacy than 400 mg bid doses. Two of the six trials (both using a 400 mg bid dose) reported null findings—one with ART-naïve participants (19), and one where ART status was not stated (23). Only one of the acyclovir studies included both males and females, but this study did not report results by sex.

Valacyclovir versus placebo

Five clinical trials that reported on HSV detection compared suppressive valacyclovir to placebo (**Table 3**). Four studies used a 500 mg bid dose (15,20,21,26), whereas one used 1,000 mg qd (25). Three studies (all using a 500 mg bid dose) reported a statistically significant protective effect of suppressive

Table 2: Summarized results for suppressive acyclovir compared to placebo

Study	Acyclovir dose	Treatment for HIV	Genital herpes simplex virus (HSV) detection			Genital HSV viral load[1]		
			Proportion treatment group	Proportion placebo group	Estimate of effect	Treatment group	Placebo group	*P* value
Cowan et al., 2008(16)	400 mg bid	Not explicitly stated	10% of visits	23% of visits	OR = 0.24 (95% CI: 0.12–0.48)			
Delany et al., 2009 (17)	400 mg bid	Not receiving ART	33% of patients	54% of patients	RR = 0.61 (95% CI: 0.46–0.80)	Mean = 3.38	Mean = 3.81	$p = 0.13$
Kim et al., 2010 (19)	400 mg bid	Not receiving ART	19.4% of patients	22.5% of patients	Not stated (but p = 0.07)	Median = 6.50	Median = 6.90	$p = 0.91$
Tanton et al., 2010 (23)	400 mg bid	Not explicitly stated	10.9% of visits	11.8% of visits	OR = 0.90 (95% CI: 0.60–1.36)	Mean = 4.16	Mean = 4.07	$p = 0.73$
Tobian et al., 2013 (24)	400 mg bid	All patients receiving ART	1.4% of visits	10.2% of visits	OR = 0.13 (95% CI: 0.04–0.41)	Median = 3.52	Median = 3.57	$p = 0.82$
Dunne et al., 2008 (18)	800 mg bid	Not receiving ART	1.6% of patients	42.4% of patients	RR = 0.00 (95% CI:.006–0.33)			

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; OR, odds ratio; RR, relative ratio

[1] Log10 copies/mL among those with detectable HSV-2 DNA

Table 3: Summarized results for suppressive valacyclovir compared to placebo

			Genital herpes simplex virus (HSV) detection			Genital HSV viral load[1]		
Study	Valacyclovir dose	Treatment for HIV	Proportion treatment group	Proportion placebo group	Estimate of effect	Treatment group	Placebo group	*P* value
Baeten et al., 2008 (15)	500 mg bid	Not receiving ART	3.7% of samples	22.1% of samples	OR = 0.13 (95% CI: 0.07–0.24)		Mean = 4.80	p = 0.002
Nagot et al., 2007 (20)	500 mg bid	Not receiving ART	4.1% of visits	17.9% of visits	RR = 0.29 (95% CI: 0.14–0.58)			
Ouedraogo et al., 2006 (21)	500 mg bid	All patients receiving highly active antiretroviral therapy (HAART)	6.6% of visits	9.8% of visits	OR = 0.37 (95% CI: 0.13–1.05)		*P* value	p = 0.12
Van Wagoner et al., 2015 (25)	1,000 mg qd	All patients receiving ART	3.8% of patients	12.5% of patients	Not stated			
Zuckerman et al., 2007 (26)	500 mg bid	Not receiving ART	4% of samples	29% of samples	Not stated (but $p < 0.001$)			

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; OR, odds ratio; RR, relative ratio

1. Log10 copies/mL among those with detectable HSV-2 DNA

valacyclovir on HSV detection (15,20,26), whereas one (also using a 500 mg bid dose) did not (21). One study (using a 1,000 mg qd dose) did not compare HSV detection between groups because of limited HSV detection in their sample (25). Of the three studies that reported a significant effect, all were in ART-naïve patients. The two studies that reported a null finding (or could not statistically compare groups) both had participants concurrently on ART. None of the valacyclovir studies sampled both males and females, and thus any differences based on sex could not be reported.

Acyclovir versus valacyclovir

One study directly compared suppressive acyclovir (400 mg bid) to a high-dose suppressive valacyclovir group (1,000 mg bid) in ART-naïve participants (22) (**Table 4**). There was no significant difference in genital HSV detection between groups. Although this study did include males and females, results were not stratified by gender.

HSV-2 viral load

Of the 12 studies that reported on genital HSV detection, 7 also reported the HSV viral load. These studies utilized PCR and reported either mean or median values for log10 copies/mL, with greater values suggestive of a potential increased risk of transmission.

Acyclovir versus placebo

Four clinical trials that compared suppressive acyclovir (400 mg bid) to placebo reported on genital HSV viral load (17,19,23,24) (**Table 2**). There were no significant differences in viral load between groups in any of these studies. Two studies had ART-naïve participants (17,19), one had patients concurrently taking ART (24), and one did not state ART status (23). Only one of the acyclovir studies included both males and females, but this study did not report results based on sex.

Valacyclovir versus placebo

Two studies that compared suppressive valacyclovir (500 mg bid) to placebo reported on genital HSV viral load (15,21) (**Table 3**). One study found valacyclovir significantly reduced viral load in ART-naïve participants (15). The other did not find a significant difference between groups in a population concurrently on highly active ART (21). Neither study sampled both sexes so differences based on sex could not be noted.

Acyclovir versus valacyclovir

Compared to high-dose suppressive valacyclovir (1,000 mg bid), suppressive acyclovir (400 mg bid) demonstrated no significant difference in viral load among ART-naïve participants (22) (**Table 4**). Although this study did include males and females, results were not stratified by sex.

Table 4: Summarized results for suppressive acyclovir compared to suppressive valacyclovir

			Genital herpes simplex virus (HSV) detection			Genital HSV viral load		
Study	Dose	Treatment for HIV	Proportion Acyclovir group	Proportion Valacyclovir group	Estimate of effect	Acyclovir treatment group	Valacyclovir treatment group	*P* value
Perti et al., 2013(22)	Valacyclovir group: 1,000 mg bid Acyclovir group: 400 mg bid	Not receiving ART	8.2% of days	7.8% of days	RR = 0.95 (95% CI: 0.66–1.37)	Median = 3.0	Median = 3.0	$p = 0.67$

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; RR, relative ratio

Adverse events

Acyclovir versus placebo

Of the seven clinical trials comparing acyclovir to placebo, only two reported on adverse events (17,23) both trials noted comparable rates in acyclovir and placebo groups. Adverse events included bacterial infections unrelated to treatment, HIV-related events, and malaria.

Valacyclovir versus placebo

Of the five studies comparing valacyclovir to placebo, four reported on adverse events. Two studies reported no serious adverse events, without going into any further detail (15,26). The remaining two studies had similar rates of adverse events in valacyclovir and placebo groups (20,25). One of these studies summarized frequencies of adverse events, with the most common being headaches (29% and 40%, in the valacyclovir group and placebo group, respectively), hypersensitivity reactions (15% and 21%), fatigue (15% and 25%), and nausea (16% and 10%)(20).

Acyclovir versus valacyclovir

The study comparing acyclovir to high-dose valacyclovir reported two adverse events related to high-dose valacyclovir (22). One participant developed urticaria and two participants with depression developed exacerbations.

Discussion

In our systematic review, only one study directly examined HSV transmission from an HIV-positive population and found no significant difference between suppressive acyclovir and placebo. Although this study had a large sample size and a lengthy follow-up period, confirmation of this finding is needed. Most studies included in this review focused on surrogate markers of HSV transmission risk, which included HSV detection and viral load. Overall, suppressive acyclovir appears to be successful in reducing HSV detection among HIV-positive populations, but it does not effectively reduce viral load. Given variations in acyclovir absorption (27), this contrary finding between HSV detection and HSV viral load may not be surprising. The effect of suppressive valacyclovir may be linked to ART status. Although this observation was based on a small sample of studies, it appears that ART may nullify the otherwise significant impact of valacyclovir therapy on HSV detection and viral load. However, this result should be interpreted with caution, as it could be confounded by the fact that individuals eligible for ART may be at a more advanced stage of HIV. In addition, the studies included in this review were not designed to specifically evaluate the impact of ART.

This systematic review provides updated information on a topic important to public health. Although previous reports assessed the impact of suppressive antiviral treatment on HSV and HIV co-infection, they were unable to specifically address HSV transmission in this population. One of the main strengths of our review is that it summarizes recent literature with a low risk of bias. In addition, all studies utilized PCR for HSV detection and viral load, overcoming the limitations of culture, which may vary more widely between studies. Based on our evaluation of the published literature, when prescribing suppressive antiviral treatment for those co-infected with HSV and HIV, clinicians should clearly articulate that treatment may not necessarily reduce risk of HSV transmission to an un-infected partner.

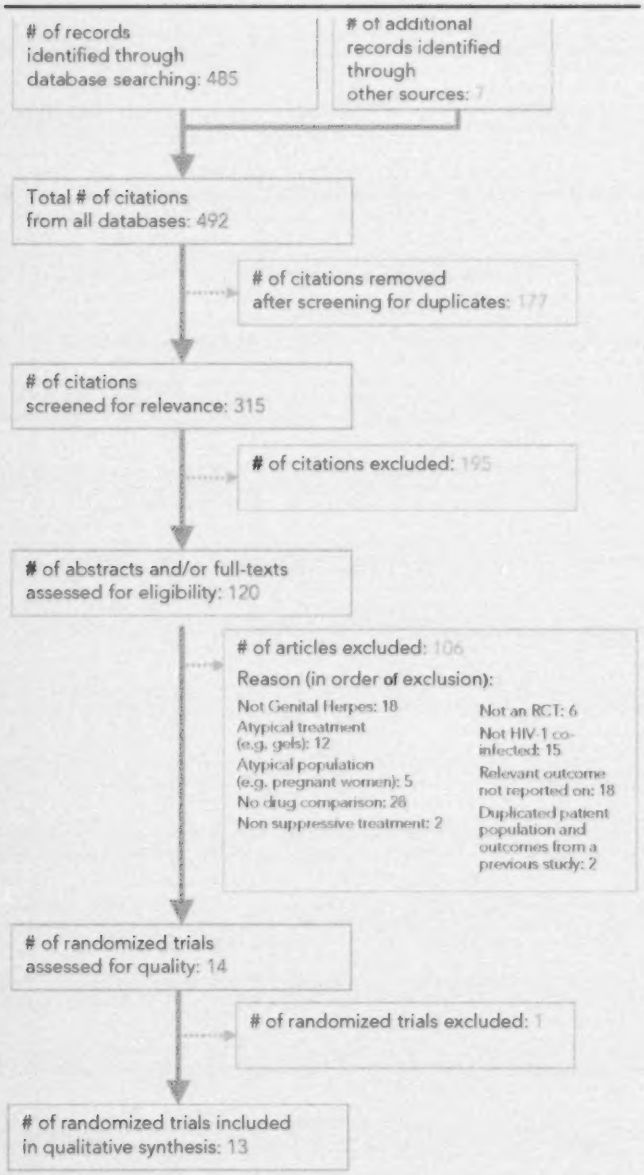
Further work is needed to confirm whether higher doses of acyclovir have a greater impact on viral load, and whether valacyclovir is only effective in ART-naïve populations. In addition, whereas resistance to acyclovir and valacyclovir is extremely low among immunocompetent populations, the resistance rate is approximately 5% in the HIV-positive population in North America (27,28). Further studies among patients with HSV and HIV are needed to address the impact of the notable level of resistance in this specific population.

Limitations of this review include the potential for publication bias and the exclusion of non-randomized controlled trials. Within the clinical trials, sample sizes, population characteristics,

types of ART, follow-up periods, and reporting methods varied. Although most studies required participants to have a

CD4 count higher than 200 cells/μL, there was variation within studies. Dosing regimens for antivirals also varied. In addition, biological measures of adherence were not used in any study; thus, reported compliance may have been inaccurate. It is also important to note that all of the studies addressing detection and viral load were powered on HIV-related outcomes, rather than the outcomes of interest in this review. As a result, it is possible that in some cases, sample sizes may have been too small to detect a difference in HSV detection or viral load. Lastly, the majority of studies were set in developing countries, with heterosexual populations; the generalizability of these results to a Canadian context and to populations of men who have sex with men may be limited.

Appendix 1: Flowchart showing selection of randomized control trials for review


# of records identified through database searching: 485
# of additional records identified through other sources: 7
Total # of citations from all databases: 492
# of citations removed after screening for duplicates: 177
# of citations screened for relevance: 315
# of citations excluded: 195
# of abstracts and/or full-texts assessed for eligibility: 120
# of articles excluded: 106
Reason (in order of exclusion):
Not Genital Herpes: 18
Atypical treatment (e.g. gels): 12
Atypical population (e.g. pregnant women): 5
No drug comparison: 26
Non suppressive treatment: 2
Not an RCT: 6
Not HIV-1 co-infected: 15
Relevant outcome not reported on: 18
Duplicated patient population and outcomes from a previous study: 2
# of randomized trials assessed for quality: 14
# of randomized trials excluded: 1
# of randomized trials included in qualitative synthesis: 13

Conclusion

Although suppressive antiviral therapies may reduce HSV detection and viral load in those with HIV co-infection, their impact on HSV transmission needs to be confirmed. When prescribing suppressive antivirals for patients with HSV and HIV co-infection, clinicians should caution patients that suppressive therapy may not reduce risk of HSV transmission to susceptible partners.

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Conflict of interest

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Impact of a social media campaign targeting men who have sex with men during an outbreak of syphilis in Winnipeg, Canada

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Abstract

Background: The city of Winnipeg has experienced a surge of infectious syphilis cases since the fall of 2012, concentrated among men who have sex with men (MSM) and who use social media technologies—including phone applications—to meet sexual contacts.

Objective: To evaluate the acceptability, cost and effectiveness of a campaign promoting syphilis testing on popular websites and applications used by MSM in the Winnipeg Health Region (WHR).

Methods: The Winnipeg Regional Health Authority developed a campaign in March 2014 highlighting the syphilis outbreak and the importance of seeking testing. Over one month, advertisements appeared on four web-platforms: Grindr, Facebook, Squirt and the Gay Ad Network. When clicked, ads would direct the user to an information website. Acceptability was assessed using the number of 'clicks' elicited by advertisements on each platform. The cost of each platform's run of advertisements was compared to the number clicks elicited to produce a cost-per-click ratio for each platform. Effectiveness was assessed by comparing the number of syphilis tests ordered for male residents of the Winnipeg Health Region in the seven-week period before and after the campaign, as well as to the same time periods in 2012 and 2013.

Results: Out of 800,000 appearances purchased, the advertisements elicited 2,166 clicks, suggesting good acceptability. Grindr and Squirt advertisements had a better cost-per-click ratio than Facebook or the Gay Ad Network. There was no significant difference in testing before (2,049 tests) versus after (2,025 tests) the campaign and these findings were similar to testing trends in 2012 and 2013.

Conclusion: Although this web-based campaign showed good acceptability and low cost, it did not appear to increase syphilis testing. This may be due to a poor campaign design; it also suggests that an education campaign alone may be insufficient to change behaviour.

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Introduction

Internet-based media have become important means for individuals to find relationship and sexual partners. A specially established infrastructure of 'hook-up' websites and smartphone applications ('apps') exists for men who have sex with men (MSM), a community of interest to public health due to their higher prevalence of certain sexually-transmitted infections (STIs). The virtualisation of the MSM community has provided important benefits, including promoting social supports and increasing access to safe sex information (1), especially among younger MSM (2). At the same time, the efficiency of 'hook-up' platforms poses challenges for public health — men who use the internet to seek sex with men consistently report a high number of recent sex partners (3-6) and those who use phone apps may be likelier to test positive for chlamydia and gonorrhea (7).

STI testing campaigns aimed at MSM are not uncommon (8), though studies have focused mainly on larger American cities with more expensive media environments (9,10). Less is known about the effectiveness of campaigns with relatively modest budgets and/or in smaller Canadian cities.

The Winnipeg Health Region is home to approximately 700,000 residents living primarily in Winnipeg, Manitoba, Canada.

Since the late 1990s, aside from two brief outbreaks in 2003 and 2007 (11,12), syphilis rates have remained relatively low in the Winnipeg Health Region. This changed in the fall of 2012, when an outbreak was declared following a surge in the number of reported infectious syphilis cases (Winnipeg Regional Health Authority, unpublished data). Two trends were clearly observable. First, the outbreak was concentrated in men, but widely spread in terms of both geographic location within the Winnipeg Health Region and age group. Second, the majority reported meeting partners through websites and apps. Faced with this, the Winnipeg Regional Health Authority (the authority overseeing care in the Winnipeg Health Region) sought to design a relatively inexpensive campaign promoting syphilis testing among local MSM. In March 2014, advertisements encouraging syphilis testing were placed on several platforms, eliciting 'clicks' to a website about syphilis. The objective of this study was to measure the acceptability, cost and effectiveness of the campaign.

Intervention

Campaign materials and management

Increased testing was felt to be a more realistic goal for a time-limited campaign rather than seeking more intensive behaviour change such as consistent condom use (13). A simple ad was developed by a local company, designed to create a sense of urgency about syphilis testing without stigmatizing or sex-negative messaging (**Figure 1**). Clicks on the ads would direct the user to a webpage featuring information about syphilis rates in Winnipeg and locations where testing could be sought. Including the design costs and media placement, the entire campaign cost approximately CAD 6,000. All dollar figures are in 2014 Canadian dollars.

Figure 1: Example of a banner ad in the "Syphilis!" testing campaign

Media platforms

Ads were hosted on four online media platforms over the month of March 2014: the Gay Ad Network, Facebook, Grindr and Squirt. The Gay Ad Network places banner ads on websites geo-targeted to gay men in a particular city or region. Although MSM use Facebook primarily to connect with face-to-face friends (2), it was chosen because of its ubiquity and ability to target ads based on users' profiles and geography. Ads on Grindr, a smartphone app for MSM that uses geolocation technology to find other users organised by physical proximity, appeared as banners across the bottom of a user's screen. Finally, Squirt is a (primarily) website-based platform wherein users create profiles and message others based on their profile information. Squirt was chosen due to its particular popularity in Winnipeg. There were two media options used with Squirt: website banner ads and an 'eblast' (a private message sent to all users' inboxes). The campaign launch was staggered due to the platforms' differing advertising cycles, but all ads were circulating by mid-March 2014 and all were wrapped up by March 31.

Outcomes

The acceptability of the campaign was defined as the extent to which users were interested enough in the ad to click on it for more information. Platforms reported the number of 'clicks' the ads received during the campaign period, which could be compared to the total number of times the ads appeared to users of that platform ('appearances').

The cost of each platform's run of ads was compared to the number of clicks elicited to determine a cost-per-click ratio for each platform.

The effectiveness of the campaign was assessed by determining whether or not there was an increase in syphilis testing among men in Winnipeg following the campaign. This was measured using data supplied by Cadham Provincial Laboratory, the public health laboratory in Manitoba that performs all of the syphilis serology testing for the province. The data included all syphilis tests performed among male residents of the Winnipeg Health Region from 2012 to the end of April 2014, based on the tester's postal code at the time of testing. The number of tests ordered in the seven-week period prior to the launch of the first ads (i.e., March 7, 2014) was compared to the number of tests ordered in the seven-week period after the first ads appeared. In addition, the number of syphilis tests ordered in the same time periods in 2012 and 2013 were examined for comparison. The association between age group (those under the age of 40, compared to those 40 years and over) and the number of tests was also assessed. Multivariable Poisson regression models were used to assess statistical significance. Stata 13 (StataCorp; College Station, Texas) was used for all analyses. Rate ratio (RR) and 95% confidence intervals were reported.

Results

Acceptability and cost

Over a period of about one month, campaign ads appeared approximately 800,000 times across all platforms and these appearances elicited 2,166 clicks to the information website. The number of clicks elicited by each platform is presented in **Table 1**, alongside the number of ad appearances and their cost. Although the Squirt 'eblast' was the most effective at eliciting clicks per thousand appearances, Grindr was by far the most successful in terms of the raw number of clicks elicited. Grindr ads were clicked 1,840 times, accounting for 85% of all campaign clicks, despite hosting only 50% of ad appearances. Clicks on Grindr were also the least expensive: for a CAD 2000 investment, the 1,840 clicks amounted to $1.09/click, followed closely by the Squirt banner ads, at $1.12/click. This suggests that the 'hook-up' platforms (Grindr and Squirt) were both the most acceptable and had the best cost-per-click ratio

Table 1: Table summarising investment (CAD), appearances and clicks for each platform

Platform	Investment	Appearances purchased	Clicks	Calculated clicks per thousand appearances	Calculated cost-per-click
Facebook square ads	$1,500.00	101,410	**22**	0.22	$68.18
Gay Ad Network banners	$1,500.00	101,520	**25**	0.25	$60.00
Squirt eblast	$477.75	4,550	**91**	20.00	$5.25
Squirt banners	$210.00	200,798	**188**	0.94	$1.12
Grindr banners	$2,000.00	~400,000	**1,840**	4.60	$1.09
TOTAL	**$5,688.00**	**808,278**	**2,166**		

Effectiveness

No difference in syphilis testing was observed in the post-campaign period. A total of 2,049 syphilis tests were performed on males resident in the Winnipeg Health Region in the seven-week period prior to the ad campaign. In comparison, 2,025 tests were performed in the post-campaign period. This slight dip is similar to trends observed in the two years previous to the campaign (**Table 2**) and so appears to be seasonal. The vast majority of tests (70%) were performed in those under the age of 40 in both time periods.

The testing rates revealed no statistically significant differences (RR: 0.99, 95%CI: 0.90-1.08; $p = .768$) when controlled for age group (<40 years and 40+ years) and year of testing (**Table 3**). Overall, those under 40 years of age were greater than 2.5 times more likely to receive syphilis testing (RR: 2.6, 95%CI: 2.5-2.7; $p < .0001$) compared with those 40 years or more. Overall, the number of syphilis tests in men increased over time by 23% from 2012 to 2014 (RR: 1.2, 95%CI: 1.2-1.3; $p < .0001$).

Without affecting overall testing numbers, advertising might still have resulted in more testing among MSM, in turn generating new cases. However, there was no significant change in the number of new reactive syphilis serologic tests detected through testing of residents in the seven-week pre- and post-campaign periods (35 and 37 reactive tests, respectively) and no increase in the number of infectious syphilis cases diagnosed (11 cases pre- and nine cases post-campaign; Winnipeg Regional Health Authority, unpublished data on file with authors).

Discussion

In a one-month period, the syphilis testing promotional campaign elicited over 2,100 clicks from the target group of MSM for an investment of less than CAD 6,000. Both the Squirt and Grindr banners were more cost-effective, at approximately $1/click. However, no relation was found between the campaign and syphilis testing rates.

The chief strength of the study is that it had access to testing data for the entire Winnipeg Health Region over multiple years, due to the centralisation of all syphilis testing within the provincial laboratory. At the same time, other aspects of the study methodology may have obscured the intervention's effects. The seven-week observation window may have been insufficient to pick up testing that occurred in response to the campaign. The laboratory data also included little about the men seeking testing other than their gender and place of residence (i.e., the inclusion criteria). It is therefore not known what proportion were MSM, obscuring whether or not this (smaller) group may have indeed sought increased testing. Future studies could consider complementary methodologies to assess changes

Table 2: Number of syphilis tests done for male residents in the Winnipeg Health Region, pre- and post- syphilis ad campaign, 2012-2014

Year	Pre-campaign period[1]			Post-campaign period[2]		
	<40 years	40+ years	Total	<40 years	40+ years	Total
2012	1,287	530	**1,817**	1,257	563	**1,820**
2013	1,369	544	**1,913**	1,327	550	**1,877**
2014	1,,442	607	**2,049**	1,424	601	**2,025**
Total	**4098**	**1,681**	**5,779**	**4,008**	**1,714**	**5,722**

[1] Pre-campaign period is defined as the seven-week period prior to implementation of the syphilis social media campaign (March 7, 2014)
[2] Post-campaign period is defined as the seven-week period post March 7, 2014

Table 3: Multivariable Poisson regression, syphilis testing frequency, Winnipeg Health Region, 2012-2014

Multivariable regression	Rate Ratio (95% Confidence Interval)	*P*-value
Pre-post comparison		
Pre-period	Reference	--
Post-period	1.00 (0.94-1.07)	0.960
Post-period, compared to pre-period (2013)	0.98 (0.89-1.07)	0.657
Post-period, compared to pre-period (2014)	0.99 (0.90-1.08)	0.768
Age group		
<40 years	Reference	--
40+ years	2.62 (2.52-2.73)	<.0001
Year		
2012	Reference	--
2013	1.15 (1.08-1.23)	<.0001
2014	1.23 (1.16-1.31)	<.0001

that may be masked by the target group's small numbers. For example, the extent to which the campaign may have increased MSM community awareness of the outbreak was not evaluated.

Several intervention factors may also explain the failure to impact testing rates. First, the ads may simply not have been effective for the audience due to aesthetic flaws or insufficient investment. Studies have documented that investment may be a crucial determinant of success, with intensive, high-coverage safer sex campaigns outperforming more inexpensive ones (9,10,14). Second, some target audience members may have missed seeing the ads because they do not have access to, or choose not to use, new technologies. Third, education campaigns do not necessarily address practical barriers to behaviour change which may have impacted some target audience members (15).

Finally, assumptions underlying the intervention may have been incorrect. Testing behaviours among MSM may already have been maximized, making the promotion of testing an inappropriate goal. The target audience may also have been too broad: while 'hook-up' websites and smartphone apps are increasingly ubiquitous among MSM, syphilis (conversely) remains relatively rare and affected by social and structural determinants (16). Emerging literature is pointing to strategies that ignore platforms or venues entirely, in favour of promoting post diagnosis testing or increasing the testing frequency of MSM who already seek regular testing (17,18).

Conclusion

Media campaigns are one public health strategy used to raise awareness among populations at increased susceptibility of a health risk. Information alone may not be enough to change behaviour. Future research should assess the combination of education campaigns with other targeted and upstream public health tactics tailored to the specific needs of the target population.

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Conflict of interest

None.

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Brief sexuality-related communication: Recommendations for a public health approach. 2015

Source: World Health Organization (WHO). Brief sexuality-related communication: Recommendations for a public health approach. 2015. http://www.who.int/reproductivehealth/publications/sexual_health/sexuality-related-communication/en/#

Sexual health is gaining more attention because of its contribution towards overall health and well-being in both adults and adolescents. Health risks arising from unsafe sexual practices and sexuality-related human rights abuses such as sexual coercion together contribute to the global burden of disease. Sexuality-related communication requires urgent attention. While clients would like their health-care providers to discuss sexual health concerns, health workers lack the necessary training and knowledge to feel comfortable addressing such issues. There is a lack of clarity in the field as to the role of sexuality communication in primary care.

The WHO set up a Guideline Development Group (GDG) which was established in June 2012 with academics, psychologists, doctors, public health specialists, lawyers and social scientists, with expertise in developing programmes or offering clinical services to promote sexual health and well-being. A systematic review was undertaken using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. The GDG developed one good practice recommendation and two policy recommendations.

The good practice recommendation is:

- Health policy-makers and decision-makers in health-care professional training institutions need to ensure that, where Brief sexuality-related communication is introduced, it respects, protects and fulfils clients' human rights.

The policy recommendations are:

- BSC is recommended for the prevention of sexually transmitted infections among adults and adolescents in primary health services (Quality of evidence: low – moderate. Strength of recommendation: strong)

- Training of health-care providers in sexual health knowledge and in the skills of brief sexuality-related communication is recommended (Quality of evidence: low – very low. Strength of recommendation: strong)

WHO plans to develop and test specific techniques of Brief sexuality-related communication to guide health-care providers in improving the quality of their care.

Useful links

World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. February 1, 2016
http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/

Public Health Agency of Canada. **Canadian Guidelines on Sexually Transmitted Infections.** http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php

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